REVIEW ARTICLE

Association of Overweight With Increased Risk of Coronary Heart Disease Partly Independent of Blood Pressure and Cholesterol Levels

A Meta-analysis of 21 Cohort Studies Including More Than 300 000 Persons

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Background: The extent to which moderate overweight (body mass index [BMI], 25.0-29.9 [calculated as weight in kilograms divided by height in meters squared]) and obesity (BMI, ≥30.0) are associated with increased risk of coronary heart disease (CHD) through adverse effects on blood pressure and cholesterol levels is unclear, as is the risk of CHD that remains after these mediating effects are considered.

Methods: Relative risks (RRs) of CHD associated with moderate overweight and obesity with and without adjustment for blood pressure and cholesterol concentrations were calculated by the members of a collaboration of prospective cohort studies of healthy, mainly white persons and pooled by means of random-effects models (RRs for categories of BMI in 14 cohorts and for continuous BMI in 21 cohorts; total N = 302 296).

Results: A total of 18 000 CHD events occurred during follow-up. The age-, sex-, physical activity–, and smoking-adjusted RRs (95% confidence intervals) for moderate overweight and obesity compared with normal weight were 1.32 (1.24-1.40) and 1.81 (1.56-2.10), respectively. Additional adjustment for blood pressure and cholesterol levels reduced the RR to 1.17 (1.11-1.23) for moderate overweight and to 1.49 (1.32-1.67) for obesity. The RR associated with a 5-unit BMI increment was 1.29 (1.22-1.35) before and 1.16 (1.11-1.21) after adjustment for blood pressure and cholesterol levels.

Conclusions: Adverse effects of overweight on blood pressure and cholesterol levels could account for about 45% of the increased risk of CHD. Even for moderate overweight, there is a significant increased risk of CHD independent of these traditional risk factors, although confounding (eg, by dietary factors) cannot be completely ruled out.

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MODERATE OVERWEIGHT (body mass index [BMI], 25.0-29.9 [calculated as weight in kilograms divided by height in meters squared]) and obesity (BMI, ≥30.0) (both henceforth called "overweight") are highly prevalent in Western populations. Nearly two-thirds of US adults[1] and 60% of Australians[2] are overweight, and increasing trends are apparent throughout the world.[3] Obesity is clearly associated with increased mortality[4,5] and adverse health outcomes, including coronary heart disease (CHD).[6]

Because of the high prevalence of overweight and the expected future increases, it is essential to gain precise insight into the consequences of overweight for health and into the metabolic pathways that link the two. This study investigated the relationship between overweight and CHD and, specifically, the extent to which this relationship is mediated by adverse effects of overweight on blood pressure and cholesterol levels. This research is relevant to clinical practice because it provides an indication about the excess risk of CHD in overweight people that would persist after optimal treatment for hypertension and hypercholesterolemia was established. Furthermore, it addresses the question whether to incorporate overweight as an additional modifiable risk factor in commonly used risk stratification schemes such as Adult Treatment Panel III or Framingham.[7,8] According to Adult Treatment Panel III, the inde-

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pendent component of risk not mediated through the major risk factors has not been quantified. Recently, cohort investigations have demonstrated that overweight is related to CHD apart from its association with traditional risk factors such as blood pressure and cholesterol levels.[9,10] Another recent publication showed that the association between overweight and death from atherosclerotic cardiovascular causes was attenuated to statistically nonsignificant levels after adjustment for blood pressure, cholesterol level, and blood glucose level.[11] An analysis based on many prospective cohort studies would add to the available evidence.

The present report describes a meta-analysis of the associations between overweight and risk of CHD for 302 296 healthy persons, mainly white. We report pooled estimates of relative risk (RR) adjusted in a standardized way from 21 prospective cohort studies that participated in a worldwide collaboration. The main outcome measure of the analysis was the age-, sex-, physical activity–, and smoking-adjusted RR of CHD, with and without adjustment for blood pressure and cholesterol levels.

METHODS

DATA SOURCES

Studies were identified by regularly checking the PubMed and MEDLINE databases, by examination of the reference lists of identified articles, and via suggestions by colleagues. An additional literature search was performed in MEDLINE (1996-2005) by using the following search strategy: *obesity*, *body mass index*, *BMI*, or *overweight* in either the title or in the Medical Subject Heading (MeSH) and either *coronary heart disease* in the title or *coronary disease* in MeSH, plus either *prospective* or *cohort*.

STUDY SELECTION

Eligible studies were prospective cohort studies conducted in healthy populations that consisted mainly of white persons for whom RRs of BMI or overweight for total incidence or mortality from CHD had been reported. We identified 70 studies that met our inclusion criteria; we were able to contact 62 investigators, and 31 of them agreed to collaborate (44% of the 70 eligible cohorts [an appendix listing the studies that were not included is available at the authors' Web site: http://www.rivm.nl/bibliotheek/digitaaldepot/appendiximd06.htm]). For the present report, it was necessary that RRs from the cohort be available with multiple adjustments for age, sex, physical activity, and smoking, both with and without simultaneous adjustment for blood pressure and cholesterol levels. Of the complete collaboration, 21 cohorts fulfilled this criterion.

DATA EXTRACTION

We requested that investigators from the participating cohort studies calculate RRs and 95% confidence intervals (CIs) with systematic univariate and multiple adjustments for age, sex, physical activity, smoking, blood pressure, and cholesterol levels. To minimize the amount of work and maximize participation, investigators could calculate the RRs of CHD in a way similar to that used in the original articles, eg, for the same BMI categories and follow-up time.

An appendix (available at the authors' Web site) presents the methods that were used in the original studies to define smoking habits, physical activity, blood pressure, and blood cholesterol level, and whether BMI was analyzed as a continuous variable or in categories. One cohort (Nurses' Health Study) used BMI based on self-reported weight and height, instead of measurements.

Adjustment for smoking was generally conducted by inclusion of dummy variables to indicate never-smokers, ex-smokers, and current smokers in the multiple regression model. For blood pressure, the majority of studies (n=15) used systolic pressure, and for blood cholesterol concentrations, total cholesterol (n=19). Other measures were, for instance, diastolic blood pressure and elevated total cholesterol concentrations (yes or no). Physical activity was predominantly defined by means of various categories of intensity, but there was considerable diversity between studies. Descriptive statistics for each cohort (eg, mean age, follow-up time, mean BMI in each category, number of persons, and cases of CHD per category) and the definition of the variables were checked by the original investigators.

DATA SYNTHESIS

Dummy variables indicated whether adjustments were made for smoking, physical activity, blood pressure, and cholesterol levels. The RRs were plotted to visualize variation in results between studies. Relative risks with equivalent adjustments were pooled by means of a random effects model[12] and were calculated for the categories moderate overweight (BMI, 25.0-29.9) and obesity (BMI, $\geq$30.0), as compared with the reference category ("normal" weight; BMI, 18.5-24.9). Studies were selected in which the foregoing definition of the overweight categories was used. In this selection, the lower limit of the normal weight category varied somewhat between cohorts (see the appendix at the author's Web site). Therefore, the meta-analysis was also performed in subsets with equal lower limits. These analyses showed that the percentage decrease in RR after adjustment for blood pressure and cholesterol levels was similar (data not shown). The final number of cohorts for the analyses of the categories moderate overweight and obesity was 14.

We also calculated risk of CHD by using BMI as a continuous variable, eg, risk per 5-unit increase in BMI. In this case, if individual studies had provided only RRs for categories of BMI, we transformed the independent variable to its continuous form for each set of adjustments by applying the method of Greenland and Longnecker,[13] but using number of cases as observed rather than their fitted values.[14] Consequently, more cohorts were available for these analyses (n=21) than for the analyses of categories of BMI.

Statistical significance of the change in RR after adjusting for blood pressure and cholesterol level was assessed by means of meta-regression analysis (in which results stemming from a single study shared the same random effect). The analyses were repeated for cohorts with measured BMI (instead of BMI based on self-reported weight and height of the participants) and cohorts in which measures for blood pressure and cholesterol concentrations were systolic blood pressure and total cholesterol concentrations (instead of, eg, diastolic blood pressure). Heterogeneity of RRs between studies was examined by χ^2 tests. All analyses were performed with the MIXED procedure in SAS statistical software, version 9 (SAS Institute Inc, Cary, NC).[15-36]

RESULTS

CHARACTERISTICS OF COHORTS

Table 1 presents characteristics of the study populations, which included a total of 302 296 persons. Most studies used either mortality from CHD or incidence of CHD (both fatal and nonfatal events) as their end point. A total of 18 000

Table 1. Characteristics of Studies Included in the Analysis

Study	Sex, % M	Age Range, y	Baseline Year(s)	Median or Mean Follow-up, y	Current Smoker, %	No. Available for Analysis	No. of Cases	End Point
Australian National Heart Foundation Risk Factor Prevalence Study[15]	49	20-70	1989-1990	8.3	24	9099	76	Death from CHD: *ICD-9* codes 410-414
Caerphilly Cohort Study[16,17a]	100	47-67	1984-1988	12	44	2160-2357	398	Fatal and nonfatal events: death from CHD; clinical nonfatal (definite acute) MI; electrocardiographic MI
Dubbo Study of Australian Elderly[18a]	44	60-94	1988	13	15	2805	968	Fatal and nonfatal events: hospitalization or death: *ICD-9-CM* codes 410-414
Finnish Mobile Clinic Health Examination Survey[19]	53	30-69	1967-1972	22	34	30 765	3319	Death from CHD: *ICD-8* codes 410-414
Fletcher Challenge[20]	72	20-89	1992	4.8	24	10 201	110	Death from CHD
Italian Rural Areas[21a]	100	40-59	1960	35	61	1622	214	Death from CHD: definite fatal MI; other forms of fatal ischemia; sudden death from CHD
Kuopio Ischaemic Heart Disease Risk Factor Study[22]	100	42-61	1984-1989	10.6	31	1597	155	Fatal and nonfatal events: definite and probable acute MI; prolonged chest pain episodes
Malmö Preventive Project[23]	100	27-61	1974-1984	17.7	49	22 025	1727	Fatal and nonfatal events: acute MI (*ICD* code 410); death from chronic CHD (*ICD* codes 412 and 414)
Melbourne Collaborative Cohort Study[24]	41	27-75	1990-1994	5.6	11	41 119	323	Death from CHD
Multifactor Primary Prevention Study, Göteborg[25]	100	47-55	1970-1973	22	50	7371	1688	Fatal and nonfatal events: death from CHD (*ICD-8/9* codes 410-414); nonfatal MI
NHANES I Epidemiologic Follow-up Study[26]	44	25-74	1971-1975	20	45	5139/5078	543	Death from CHD: *ICD-9* codes 410-414.9
Nijmegen Cohort Study[27]	48	20-52	1977-1978	18	58	5898	268	Fatal and nonfatal events: MI; angina pectoris
Norwegian Counties Study[28]	51	35-49	1974-1978	26	45	43 896	1564	Death from CHD: *ICD-8/9* codes 410-414, *ICD-10* codes I21-I25; sudden deaths (*ICD-8* codes 782.4 and 795; *ICD-9* codes 798.1-798.2; *ICD-10* code R96)
Nurses' Health Study[29b]	0	34-59	1980	20	28	76 615	1996	Fatal and nonfatal events: death from CHD; nonfatal MI; sudden death within 1 h of onset of symptoms in women with no plausible cause other than CHD
PRIME Study[30a]	100	50-59	1991-1993	5	28	9757	317	Fatal and nonfatal events: MI; death from CHD; angina pectoris
Rome Railroad Cohort[31a]	100	40-59	1962	25	66	726	88	Death from CHD: definite fatal MI; sudden death from CHD; cases judged of CHD origin although manifested only as heart failure, arrhythmia, and blocks
Scottish Heart Health Study[32]	51	40-59	1984-1987	7.6	39	10 262	171	Fatal and nonfatal events: MI; coronary artery surgery; death from CHD
US Railroad Cohort[31a]	100	40-59	1957-1959	25	60	2415	481	Death from CHD: definite fatal MI; sudden death from CHD; cases judged of CHD origin although manifested only as heart failure, arrhythmia, and blocks
Ventimiglia di Sicilia Heart Study[33a]	43	20-69	1989	8	17	835	8	Death from CHD: defined MI; sudden death
Whitehall Study[34,35]	100	40-64	1967-1969	33	41	17 475	3503	Death from CHD: *ICD-8* codes 410-414
Zutphen Elderly Study[36]	100	64-84	1985	10.3	33	575	83	Death from CHD: *ICD-9* codes 410-414

Abbreviations: CHD, coronary heart disease; *ICD, International Classification of Disease* (-8, -9, and -10 indicate the revision number; *CM, Clinical Modification*); MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; PRIME, Prospective Epidemiological Study of Myocardial Infarction.

[a] No results available for both the categories moderate overweight (body mass index, 25.0-29.9 [calculated as weight in kilograms divided by height in meters squared]) and obesity (body mass index, ≥30.0).

[b] Body mass index based on self-report of the participants.

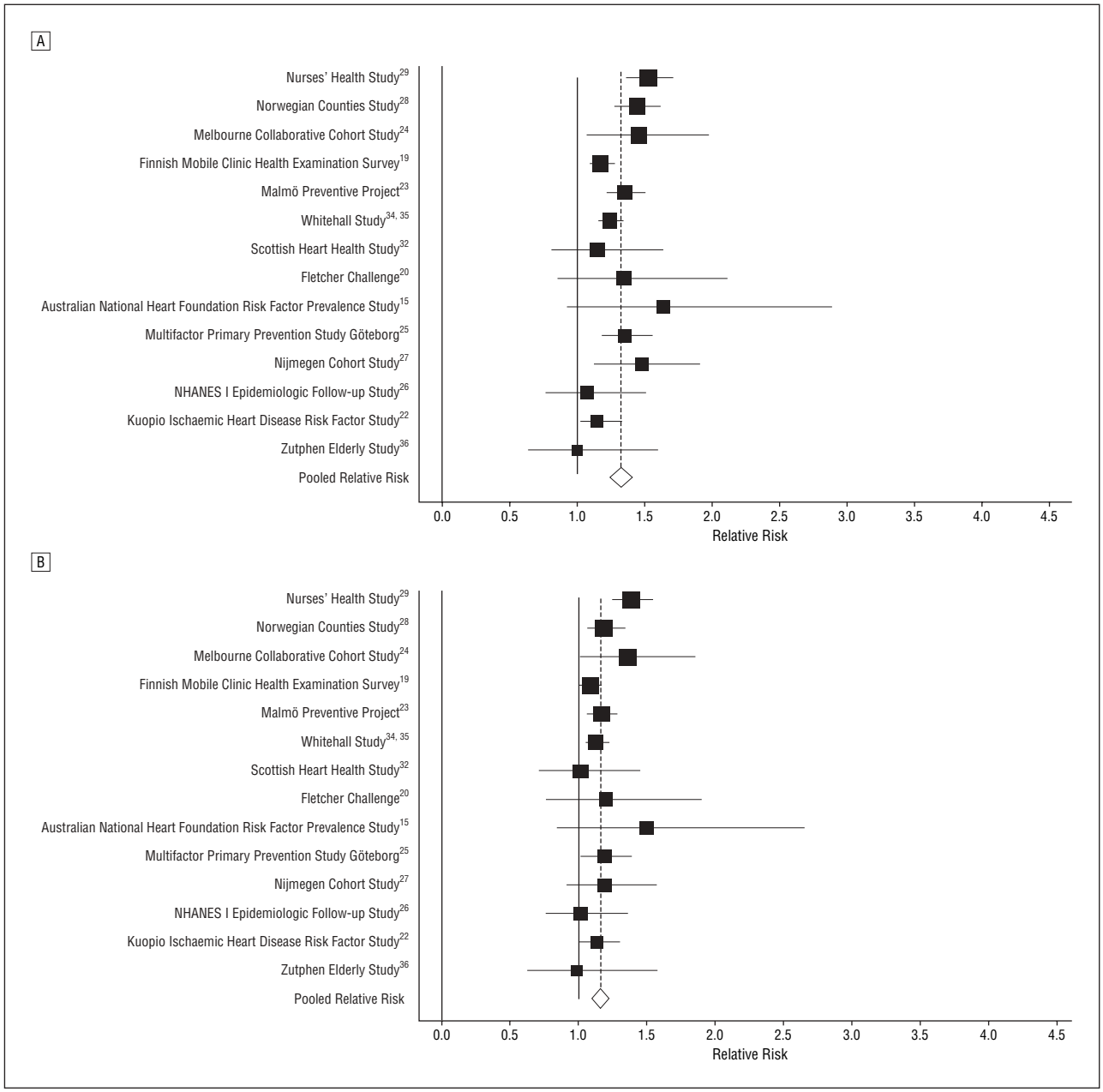

Figure 1. Relative risks of coronary heart disease for moderate overweight (body mass index [calculated as weight in kilograms divided by height in meters squared], 25.0-29.9) adjusted for age, sex, smoking, and physical activity (A) and additionally adjusted for blood pressure and cholesterol concentrations (B), sorted by descending study size (reflected by the size of the square). Limit lines indicate the 95% confidence interval. NHANES indicates National Health and Nutrition Examination Survey.

CHD events were observed during follow-up. We were able to extend follow-up for some studies beyond that reported in the original articles. Table 1 presents the data as used in the present analysis.

RRs FOR MODERATE OVERWEIGHT AND OBESITY

Figure 1 and **Figure 2** present the RRs of CHD for the separate cohorts for categories of moderate overweight and obesity, adjusted for age, sex, physical activity, and smoking, with and without adjustment for blood pressure and cholesterol levels. In all individual studies, the RR decreased after adjustment for blood pressure and cholesterol concentrations.

Table 2 presents pooled RRs of CHD for categories of BMI. After adjustment for age, sex, physical activity, and smoking, moderate overweight was associated with an RR of 1.32 (95% CI, 1.24-1.40) and obesity with an RR of 1.81 (95% CI, 1.56-2.10). Additional adjustment for blood pressure and cholesterol levels statistically significantly reduced the RR to 1.17 (95% CI, 1.11-1.23) for moderate overweight and 1.49 (95% CI, 1.32-1.67) for obesity. This corresponds to a decrease in excess risk of 47% for moderate overweight and 40% for obesity, ie, $[(1.81-1.49)/(1.81-1)]\times 100=40\%$.

The RRs were similar for studies in which BMI was measured (n=13) instead of based on self-reported weight and height, and for studies

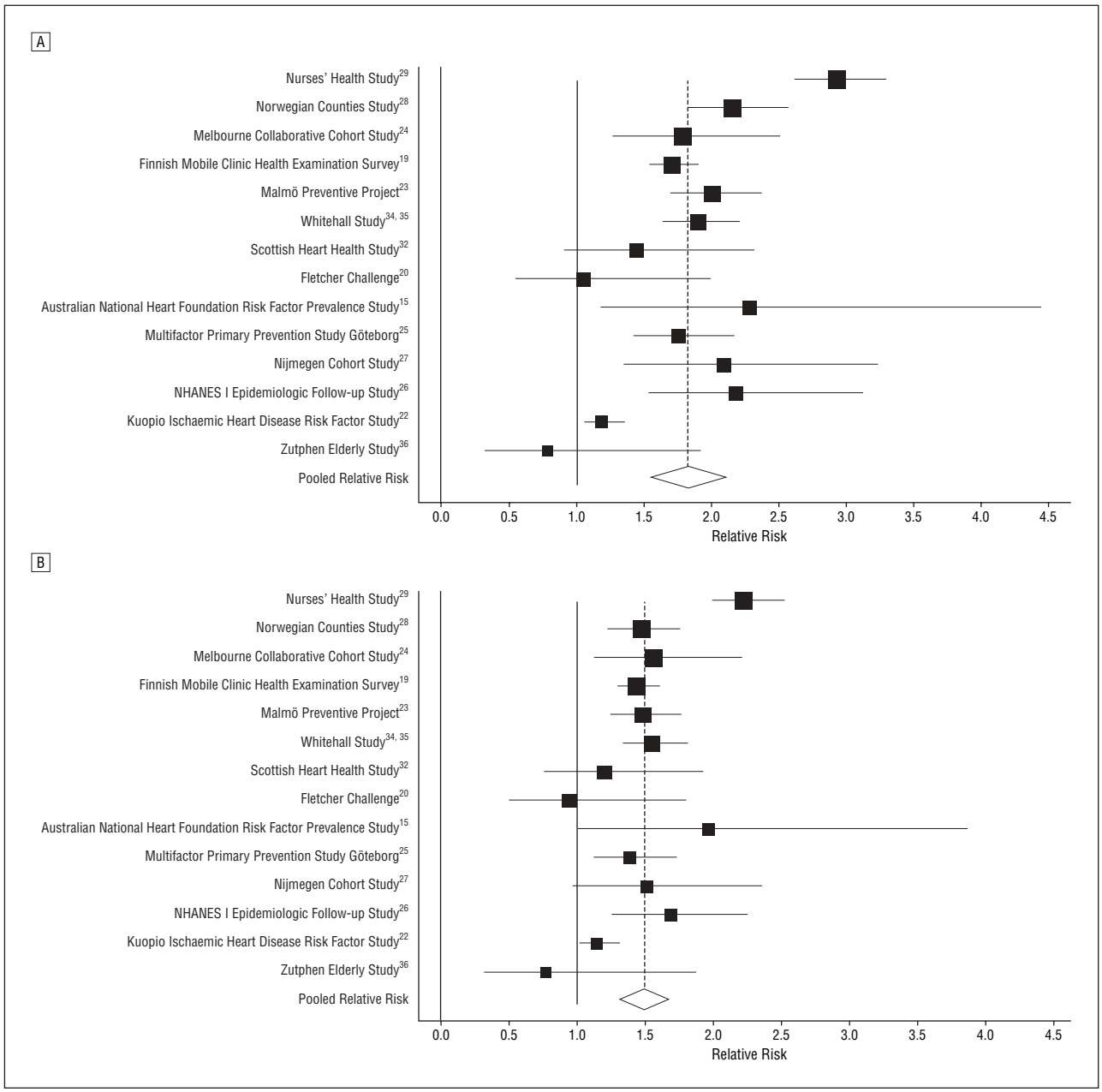

Figure 2. Relative risks of coronary heart disease for obesity (body mass index [calculated as weight in kilograms divided by height in meters squared], ≥30.0) adjusted for age, sex, smoking, and physical activity (A) and additionally adjusted for blood pressure and cholesterol concentrations (B), sorted by descending study size (reflected by the size of the square). Limit lines indicate the 95% confidence interval. NHANES indicates National Health and Nutrition Examination Survey.

in which BMI was measured and adjustments were made for systolic blood pressure and total cholesterol levels (n=11; instead of other indicators such as diastolic blood pressure [the appendix at the authors' Web site] shows which measures of blood pressure and cholesterol levels were used]). In the latter subset of studies, the risk of CHD decreased statistically significantly by 50% for moderate overweight and 43% for obesity after additional adjustment for blood pressure and cholesterol levels.

RR ASSOCIATED WITH A 5-UNIT INCREASE IN BMI

When BMI was analyzed as a continuous variable, the age-, sex-, physical activity–, and smoking-adjusted RR associated with a 5-unit increase was 1.29 (95% CI, 1.22-1.35; n=21; **Table 3**). After excluding participants with a BMI less than 20, this RR was similar (n=6 studies, not shown). The range between studies was 0.95 to 1.73. Additional adjustment for blood pressure and cholesterol level lowered the excess risk by 45% to 1.16 (95% CI, 1.11-1.21; range, 0.83-1.87). Significant heterogeneity existed between studies both with and without adjustment for blood pressure and cholesterol concentrations ($P<.001$).

COMMENT

In this large meta-analysis, involving 302 296 participants worldwide and 18 000 CHD events during follow-up, a 5-unit increment in BMI

Table 2. Relative Risks (RRs) of Coronary Heart Disease for Moderate Overweight and Obesity Compared With Normal Weight[a] With and Without Adjustments for Blood Pressure and Cholesterol Levels

Selection (No. of Studies)	RR (95% CI) for Moderate Overweight	*P* Value for Heterogeneity[b]	RR (95% CI) for Obesity	*P* Value for Heterogeneity[b]
		Adjusted for Age, Sex, Physical Activity, and Smoking		
All studies (14)	1.32 (1.24-1.40)	.007	1.81 (1.56-2.10)	<.001
BMI measured (13)	1.29 (1.22-1.37)	.12	1.72 (1.52-1.96)	<.001
BMI measured, systolic blood pressure and total cholesterol (11)[c]	1.32 (1.24-1.40)	.26	1.69 (1.45-1.97)	<.001
		Additionally Adjusted for Blood Pressure and Cholesterol		
All studies (14)	1.17 (1.11-1.23)[d]	.15	1.49 (1.32-1.67)[d]	<.001
BMI measured (13)	1.14 (1.09-1.18)[d]	.88	1.41 (1.31-1.53)[d]	.11
BMI measured, systolic blood pressure and total cholesterol (11)[c]	1.16 (1.11-1.21)[d]	.96	1.39 (1.26-1.53)[d]	.10

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval.
[a] For each study's definition of normal weight, see the appendix available at http://www.rivm.nl/bibliotheek/digitaaldepot/appendiximd06.htm; moderate overweight, BMI of 25.0 to 29.9; obesity, BMI of 30.0 or more.
[b] *P* value for heterogeneity in RR between studies.
[c] For these studies, the RRs are adjusted for systolic blood pressure (instead of other indicators such as diastolic blood pressure) and total cholesterol concentrations (instead of other indicators of cholesterol).
[d] $P < .001$ for difference in RR with and without adjustment for blood pressure and cholesterol level.

Table 3. Relative Risks (RRs) of Coronary Heart Disease per 5-Unit Increase in BMI With and Without Adjustments for Blood Pressure and Cholesterol Levels

Selection (No. of Studies)	RR (95% CI) Adjusted for Age, Sex, Physical Activity, and Smoking	*P* Value for Heterogeneity[a]	RR (95% CI) Additionally Adjusted for Blood Pressure and Cholesterol	*P* Value	
				Heterogeneity[a]	Difference[b]
All studies (21)	1.29 (1.22-1.35)	<.001	1.16 (1.11-1.21)	<.001	<.001
BMI measured (20)	1.27 (1.21-1.33)	<.001	1.15 (1.11-1.19)	.04	<.001
BMI measured, systolic blood pressure and total cholesterol (15)[c]	1.28 (1.20-1.36)	<.001	1.15 (1.11-1.20)	.04	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval.
[a] *P* value for heterogeneity in RR between studies.
[b] *P* value for difference in RRs with and without adjustment for blood pressure and cholesterol level.
[c] In the last 2 columns, the RRs are adjusted for systolic blood pressure (instead of other indicators such as diastolic blood pressure) and total cholesterol concentrations (instead of other indicators of cholesterol).

was associated with a 29% increase in risk of CHD and, after additional adjustment for blood pressure and cholesterol levels, with a 16% increased risk. Hence, the present study indicates that adverse effects of overweight on blood pressure and cholesterol levels could account for about 45% of the increased risk of CHD, and that there is still a significantly increased risk of CHD that is independent of these effects.

The strength of our analysis lies in the large number of cohorts and the systematic adjustments for relevant variables. It is clearly shown that adjusting for blood pressure and cholesterol decreases the estimated RR of CHD substantially. This was the case in all studies, despite the observed heterogeneity in RRs. Meta-regression analysis suggests that causes of heterogeneity are the age of the population and the follow-up time, but not, for example, the end point that was used (fatal and nonfatal incidence vs mortality of CHD) (data not shown). We did not exclude the first years of follow-up in our analysis to account for undiagnosed preexisting disease that may cause weight loss and death, leading to a J-shaped BMI-mortality curve. Previous research showed that this effect of excluding early deaths is only marginal.[37] In general, publication bias, ie, less frequent publication of studies with absent or negative associations between BMI and CHD, could have increased the apparent RR. An indication for the absence of publication bias (as suggested by a funnel plot; not shown) is that studies with higher estimates of RR were not overrepresented among the studies with low precision (ie, the smaller studies). Furthermore, the decision to participate in the collaboration seemed to depend merely on practical issues, such as time needed to conduct the analyses, and not on the actual results of a study. The majority of the eligible studies not included in our analysis also reported positive associations between moderate overweight and obesity and the risk of CHD, although the results were not always statistically significant. (An overview of these results from the literature is available at the authors' Web site).

The present study has 2 important implications. First, even moderate overweight is associated with increased risk of CHD (for obesity

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this was already no point of debate). Because high blood pressure and cholesterol levels are plausible intermediary factors in the causal pathways linking overweight and CHD,[6] adjusting for them—in epidemiological analyses—certainly results in underestimating the total public health impact of overweight. Second, the fact that the RR of CHD remained statistically significant after adjustment for these intermediary factors adds to the evidence that overweight itself increases CHD risk independent of traditional risk factors. This implies that, even under the theoretical scenario that optimal treatment would be available against hypertension and hypercholesterolemia in overweight persons, they still would have an elevated risk of CHD. It also implies that overweight, which is easily measured, may be considered to be incorporated as an additional risk factor in commonly used risk stratification schemes such as Adult Treatment Panel III[7] and the Framingham CHD prediction algorithm,[8] even though the exact mechanism that underlies an "independent" effect remains to be resolved.

The present estimate of the RR adjusted for blood pressure and cholesterol level, ie, 1.16 per 5 BMI units, is similar to the recently reported RR of hospitalization for CHD of 1.16 per 4 BMI units after adjustment for smoking, systolic blood pressure, and total cholesterol level.[9] Because hypertension is correlated with other features of the metabolic syndrome, such as fasting serum glucose level,[11,38] part of the reduction in the RR after adjustment for blood pressure may be caused by adjustment for these correlated variables, resulting in an overestimate of the excess risk of CHD mediated by blood pressure and cholesterol concentrations. On the other hand, the use of a single measurement of blood pressure and cholesterol, as opposed to repeated measurements, may have underestimated the effect of adjustment for these variables.[39]

Several mechanisms could underlie an effect of overweight on CHD independent of traditional risk factors. These include a state of low-grade inflammation, endothelial dysfunction, hemostatic imbalance favoring coagulation, impaired endothelial vasodilatory responses, left ventricular hypertrophy due to an increased blood volume, and reduced heart rate variability due to withdrawal of vagal activity and sympathetic predominance.[40] Obviously, overweight is associated with increased risk of type 2 diabetes mellitus.[41] In Adult Treatment Panel III, obesity is not listed as a risk factor because it is said to operate through diabetes (and other risk factors).[7] Therefore, inclusion of data on diabetes or glucose intolerance in

our analysis (which were not available for the meta-analysis) would have further attenuated the RR of CHD associated with overweight. Indeed, a large Korean cohort study[11] showed that the RR of death from atherosclerotic cardiovascular causes decreased considerably after adjustment for blood pressure, cholesterol level, and fasting blood glucose level. Interestingly, the authors stated that, in addition to these factors, other consequences of increased BMI are likely to contribute to the risk of cardiovascular disease.

Before invoking the plausible pathways mentioned previously, some alternative explanations for our findings must be mentioned. There may have been confounders for which we were unable to adjust, and that themselves, rather than overweight, determine the risk of CHD. For instance, we did not control for diet, which has been shown to be related to CHD,[42] because detailed dietary data were usually not available. However, in the Nurses' Health Study—the largest study included—adjustment for diet had virtually no impact on the association between BMI and risk of CHD.[29] Also, the possibility of residual confounding due to inaccurate assessment of smoking and physical activity cannot be excluded. Despite diversity in the assessment of physical activity, most studies used measures that discerned between low and at least moderate levels of activity and, in most studies, additional adjustment for physical activity did not substantially change the age-, sex-, and smoking-adjusted RRs substantially (data not shown), which might indicate that measurement error did not differ much between studies.

With respect to the measure of body fatness used, waist-to-hip ratio has been shown to be more strongly related to CHD.[43,44] The INTERHEART study demonstrated a graded and highly significant association between myocardial infarction and waist-to-hip ratio, in contrast to BMI.[43] However, that study had a cross-sectional case-control design, and the long-term influence of factors such as overweight in midlife therefore could not be assessed. Furthermore, BMI is by far the most common measure of body fatness, especially in cohort studies that started decades ago, and therefore is most suitable for a meta-analysis. The present findings apply to healthy persons, predominantly white. A meta-analysis of cohorts in the Asia-Pacific region showed that risk of cardiovascular disease and CHD increased linearly from BMI levels as low as 18.[45] It is known that in Asians the risk of CHD is increased at lower levels of BMI than in whites[46] and hence confirmation in primarily white populations was warranted. Our results are similar to those of a previous systematic review[47] that included mainly white cohorts, which found a RR of 1.14 per 2 BMI units. However, no formal meta-analysis was attempted in that study, and there was more variation between cohorts in the covariates for which the RRs were adjusted.

We conclude that moderate overweight and obesity are associated with a significant increase in risk of CHD, and thus that the worldwide increase in (moderate) overweight may drive the incidence of CHD upward. Although effects of confounders, such as specific dietary factors, cannot be completely ruled out, negative effects will be exerted both through adverse influences on blood pressure and cholesterol levels (accounting for approximately 45% of the increased risk) and through other pathways.

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